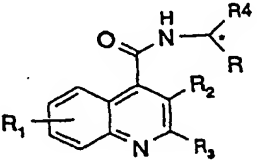


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<p>(21) International Application Number: PCT/EP99/09156 (22) International Filing Date: 22 November 1999 (22.11.99) (30) Priority Data: 9825554.0 20 November 1998 (20.11.98) GB (71) Applicants (for all designated States except US): SMITHKLINE BEECHAM S.P.A. [IT/IT]; Via Zambelletti, I-20021 Baranzate di Bollate (IT). SMITHKLINE BEECHAM LABORATOIRES PHARMACEUTIQUES [FR/FR]; 6, esplanade Charles de Gaulle, F-92731 Nanterre Cedex (FR). (72) Inventors; and (75) Inventors/Applicants (for US only): FARINA, Carlo [IT/IT]; SmithKline Beecham S.p.A., Via Zambelletti, I-20021 Baranzate di Bollate (IT). GIARDINA, Giuseppe [IT/IT]; SmithKline Beecham S.p.A., Via Zambelletti, I-20021 Baranzate di Bollate (IT). GRUGNI, Mario [IT/IT]; SmithKline Beecham S.p.A., Via Zambelletti, I-20021 Baranzate di Bollate (IT). NADLER, Guy, Marguerite, Marie, Gerard [FR/FR]; SmithKline Beecham Laboratoires Pharmaceutiques, Unité de Recherche, 4, rue de Chesnay-Beauregard, Boîte postale 58, F-35762 St Gregoire</p>	<p>(FR). RAVEGLIA, Luca, Francesco [IT/IT]; SmithKline Beecham S.p.A., Via Zambelletti, I-20021 Baranzate di Bollate (IT). (74) Agent: RUTTER, Keith; Corporate Intellectual Property, SmithKline Beecham, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). <b>Published</b> With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>	
<p>(54) Title: QUINOLINE DERIVATIVES AS NK-2 AND NK-3 RECEPTOR LIGANDS</p> <div style="text-align: center;">  <p>(I)</p> </div> <p>(57) Abstract</p> <p>A compound, or a solvate or a salt thereof, of formula (I), wherein R is linear or branched alkyl; R<sub>1</sub> represents hydrogen or up to four optional substituents selected from the list consisting of: C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkenyl, aryl, C<sub>1-6</sub> alkoxy, hydroxy, halogen, nitro, cyano, carboxy, carboxamido, sulphonamido, C<sub>1-6</sub> alkoxy-carbonyl, trifluoromethyl, acyloxy, phthalimido, amino or mono- and di-C<sub>1-6</sub> alkylamino; R<sub>2</sub> represents a moiety -(CH<sub>2</sub>)<sub>n</sub>-NY<sub>1</sub>Y<sub>2</sub> wherein n is an integer in the range of from 1 to 9, Y<sub>1</sub> and Y<sub>2</sub> are independently selected from hydrogen; C<sub>1-6</sub>-alkyl; C<sub>1-6</sub> alkyl substituted with hydroxy, C<sub>1-6</sub> alkylamino or bis (C<sub>1-6</sub> alkyl) amino; C<sub>1-6</sub>-alkenyl; aryl or aryl-C<sub>1-6</sub>-alkyl or Y<sub>1</sub> or Y<sub>2</sub> together with the nitrogen atom to which they are attached represent an optionally substituted N-linked single or fused ring heterocyclic group; R<sub>3</sub> is branched or linear C<sub>1-6</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>4-7</sub> cycloalkylalkyl, optionally substituted aryl, or an optionally substituted single or fused ring aromatic heterocyclic group; and R<sub>4</sub> represents hydrogen or alkyl or R<sub>4</sub> and R together with the carbon atom to which they are attached form an optionally substituted C<sub>3-12</sub> cycloalkyl group; a process for preparing such compounds, a pharmaceutical composition comprising such compounds and the use of such compounds as NK-2 or NK-3 receptor ligands.</p>		

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## QUINOLINE DERIVATIVES AS NK-2 AND NK-3 RECEPTOR LIGANDS

The present invention relates to novel compounds, in particular to novel quinoline derivatives, to processes for the preparation of such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds in medicine.

The mammalian peptide Neurokinin B (NKB) belongs to the Tachykinin (TK) peptide family which also include Substance P (SP) and Neurokinin A (NKA). Pharmacological and molecular biological evidence has shown the existence of three subtypes of TK receptor (NK<sub>1</sub>, NK<sub>2</sub> and NK<sub>3</sub>) and NKB binds preferentially to the NK<sub>3</sub> receptor although it also recognises the other two receptors with lower affinity (Maggi et al, 1993, *J. Auton. Pharmacol.*, 13, 23-93).

Selective peptidic NK<sub>3</sub> receptor antagonists are known (Drapeau, 1990 *Regul. Pept.*, 31, 125-135), and findings with peptidic NK<sub>3</sub> receptor agonists suggest that NKB, by activating the NK<sub>3</sub> receptor, has a key role in the modulation of neural input in airways, skin, spinal cord and nigro-striatal pathways (Myers and Udem, 1993, *J. Physiol.*, 470, 665-679; Counture et al., 1993, *Regul. Peptides*, 46, 426-429; Mccarson and Krause, 1994, *J. Neurosci.*, 14 (2), 712-720; Arenas et al. 1991, *J. Neurosci.*, 11, 2332-8). However, the peptide-like nature of the known antagonists makes them likely to be too labile from a metabolic point of view to serve as practical therapeutic agents.

Copending International Patent Application number PCT/EP98/03014 discloses certain compounds stated to be non-peptide NK-3 antagonists and also to have NK-2 antagonist activity. These compounds are therefore considered to be of potential use in the prevention and treatment of a wide variety of clinical conditions which are characterized by overstimulation of the tachykinin receptors, in particular NK-3 and NK-2.

We have now discovered a novel class of non-peptide compounds having NK-3 antagonist activity which are far more stable from a metabolic point of view than the known peptidic NK-3 receptor antagonists and are of potential therapeutic utility. Surprisingly however, the present compounds show greater affinity for the NK-2 receptor than for the NK-3 receptor. Thus, although these compounds are considered to be of potential use in the prevention and treatment of a wide variety of clinical conditions which are characterized by overstimulation of the tachykinin receptors, in particular NK-3 and NK-2, they are considered to be of use in those therapeutic areas characterised primarily by overstimulation of the NK-2 receptor, for example the pulmonary area (especially useful in the treatment of the bronchospastic and inflammatory component of asthma, coughing and pulmonary irritation), the gastro-intestinal tract area (especially useful in the treatment of intestinal spasms and

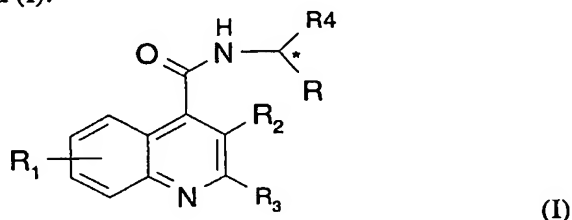
GI tract disorders including irritable bowel syndrome and gastro-exophageous reflex disease) the inflammatory and tissue repair area (especially useful in the treatment of syndromes associated with bladder disfunctions including urinary incontinence; or inflammatory processes of bladder and ureter associated with cystitis, kidney infections and colics and spasms of the biliary tract; rheumatoid arthritis) (hereinafter referred to as the "NK-2 Conditions").

These compounds are also useful for treating respiratory diseases, such as chronic obstructive pulmonary disease (COPD), asthma, airway hyperreactivity, cough; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis, rheumatoid arthritis and inflammatory pain; neurogenic inflammation or peripheral neuropathy, allergies such as eczema and rhinitis; ophthalmic diseases such as ocular inflammation, conjunctivitis, vernal conjunctivitis and the like; cutaneous diseases, skin disorders and itch, such as cutaneous wheal and flare, contact dermatitis, atopic dermatitis, urticaria and other eczematoid dermatitis; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosus; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease, irritable bowel syndrome (IBS), gastro-exophageous reflex disease (GERD); urinary incontinence and disorders of the bladder function; renal (hereinafter referred to as the 'Primary Conditions'). The "Primary Conditions" also include the "NK-2 Conditions")

Certain of these compounds also show CNS activity and hence are considered to be of particular use in the treatment of disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; neurodegenerative disorders such as AIDS related dementia, senile dementia of the Alzheimer type, Alzheimer's disease, Down's syndrome, Huntington's disease, Parkinson's disease, movement disorders and convulsive disorders (for example epilepsy); demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis and other neuropathological disorders such as diabetic neuropathy, AIDS related neuropathy, chemotherapy-induced neuropathy and neuralgia; addiction disorders such as alcoholism; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; eating disorders (such as food intake disease); fibrosing and collagen diseases such as scleroderma and eosinophilic fasciitis; disorders of the blood flow caused by vasodilation and vasospastic diseases such as angina, migraine and Reynaud's disease and pain or nociception, for example, that is attributable to or associated with any of the foregoing conditions especially the transmission of pain in migraine, (hereinafter referred to as the 'Secondary Conditions').

The compounds of formula (I) are also considered to be useful as diagnostic tools for assessing the degree to which neurokinin-3 and neurokinin-2 receptor activity (normal, overactivity or underactivity) is implicated in a patient's symptoms.

According to the present invention there is provided a compound, or a solvate or a salt thereof, of formula (I):



wherein R is linear or branched alkyl ;

R<sub>1</sub> represents hydrogen or up to four optional substituents selected from the list consisting of: C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkenyl, aryl, C<sub>1-6</sub> alkoxy, hydroxy, halogen, nitro, cyano, carboxy, carboxamido, sulphonamido, C<sub>1-6</sub> alkoxycarbonyl, trifluoromethyl, acyloxy, phthalimido, amino or mono- and di-C<sub>1-6</sub> alkylamino;

R<sub>2</sub> represents a moiety  $-(CH_2)_n-NY_1Y_2$  wherein n is an integer in the range of from 1 to 9, Y<sub>1</sub> and Y<sub>2</sub> are independently selected from C<sub>1-6</sub>-alkyl; C<sub>1-6</sub> alkyl substituted with hydroxy, alkoxy, C<sub>1-6</sub> alkylamino or bis (C<sub>1-6</sub> alkyl) amino; C<sub>3-6</sub> cycloalkyl; C<sub>4-6</sub> azacycloalkyl; C<sub>1-6</sub>-alkenyl; aryl or aryl-C<sub>1-6</sub>-alkyl or Y<sub>1</sub> and Y<sub>2</sub> together with the nitrogen atom to which they are attached represent an optionally substituted N-linked single or fused ring heterocyclic group;

R<sub>3</sub> is branched or linear C<sub>1-6</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>4-7</sub> cycloalkylalkyl, optionally substituted aryl, or an optionally substituted single or fused ring aromatic heterocyclic group; and

R<sub>4</sub> represents hydrogen or alkyl or R<sub>4</sub> and R together with the carbon atom to which they are attached form an optionally substituted C<sub>3-12</sub> cycloalkyl group .

Suitable optionally substituted C<sub>3-12</sub> cycloalkyl groups include C<sub>3-12</sub> cycloalkyl groups, especially C<sub>4-7</sub> cycloalkyl groups, for example a C<sub>5</sub> or C<sub>6</sub> cycloalkyl group, fused to other cycloalkyl groups or fused to C<sub>3-12</sub> cycloalkyl groups fused to aryl.

Suitable C<sub>3-12</sub> cycloalkyl groups fused to other cycloalkyl groups include C<sub>4-12</sub>, cycloalkyl groups, especially C<sub>5</sub> and C<sub>6</sub> cycloalkylgroups, fused to other C<sub>3-12</sub> cycloalkyl groups, especially C<sub>5</sub> and C<sub>6</sub> cycloalkylgroups; examples of such groups include 2-adamantyl and bicyclo[2.2.1]heptan-2-yl.

Suitable C<sub>3-12</sub> cycloalkyl groups fused to aryl groups, include C<sub>4-12</sub>, cycloalkyl groups, especially C<sub>5</sub> and C<sub>6</sub> cycloalkylgroups, fused to one or more benzene rings; examples of such groups include indan-1-yl, indan-2-yl or a 1, 2, 3, 4 - tetrahydronaphthalen-1-yl groups.

Suitably, R represents C<sub>1-6</sub> alkyl, for example methyl, ethyl, iso-propyl or ter-butyl.

Preferably R represents ter-butyl.

Suitably, R<sub>4</sub> is C<sub>1-6</sub> alkyl, for example methyl.

Suitably, R<sub>3</sub> is optionally substituted aryl, preferably an unsubstituted aryl group such as a phenyl group.

Suitably R<sub>1</sub> represents hydrogen, C<sub>1-6</sub> alkoxy, for example methoxy, or hydroxy.

Preferably, R<sub>1</sub> represents hydrogen.

Suitably, NY<sub>1</sub>Y<sub>2</sub> represents an optionally substituted N-linked single or fused ring heterocyclic group.

Suitable N-linked single or fused heterocyclic groups, include groups in which any single or fused ring is saturated or unsaturated and consists of 5- or 6- ring atoms, said ring atoms optionally comprising 1 or 2 additional heteroatoms selected from O or N and wherein one or two ring atoms are optionally substituted with one or two oxo groups or one or two of hydroxy, carboxy, carboxy C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxycarbonyl, aminocarbonyl, C<sub>1-6</sub> alkylcarbonyl optionally substituted with an aromatic heterocyclic group, arylcarbonyl, aryl C<sub>1-6</sub> alkylcarbonyl, carboxy C<sub>1-6</sub> alkylcarbonyl, carboxyarylcarbonyl, amino, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> hydroxyalkyl, aryl, aryl, C<sub>1-6</sub> alkyl, C<sub>3-7</sub> cycloalkyl, optionally substituted C<sub>4-7</sub> cycloalkenyl, optionally substituted C<sub>4-7</sub> azacycloalkyl, optionally substituted C<sub>4-7</sub> diazacycloalkyl, optionally substituted C<sub>4-7</sub> oxazacycloalkyl, optionally substituted C<sub>4-7</sub> thiazacycloalkyl, optionally substituted C<sub>4-7</sub> thiazacycloalkenyl, C<sub>3-7</sub> cycloalkylalkyl, hydroxy C<sub>1-6</sub> alkoxy C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy C<sub>1-6</sub> alkyl, di C<sub>1-6</sub> alkylaminocarbonyl, di C<sub>1-6</sub> alkylamino C<sub>1-6</sub> alkylcarbonyl, optionally substituted C<sub>4-7</sub> azacycloalkyl C<sub>1-6</sub> alkylcarbonyl, optionally substituted C<sub>4-7</sub> diazacycloalkyl C<sub>1-6</sub> alkylcarbonyl, optionally substituted C<sub>4-7</sub> oxazacycloalkyl C<sub>1-6</sub> alkylcarbonyl, optionally substituted carboxamidine, C<sub>1-6</sub> alkylaminothiocarbonyl, optionally substituted nitrovinyl, aminosulphonyl, di C<sub>1-6</sub> alkylaminosulphonyl, or an optionally substituted spiroheterocyclic ring or a single or fused ring aromatic heterocyclic group, or the substituents on adjacent ring atoms form a carbocyclic ring; said aryl or aromatic heterocyclic groups being optionally substituted with one or two C<sub>1-6</sub> alkyl, alkoxy, hydroxy, halogen or halogenalkyl groups; wherein, unless otherwise defined optionally substituted means substituted with up to three substituents selected from the list consisting of: amino, alkylamino, alkyl, aryl, heterocyclyl, alkylaryl, aralkyl, oxo, hydroxy, nitrile.

Preferably, the additional heteroatom is N.

Favoured optional substituents for the N-linked single or fused heterocyclic groups are selected from carboxy C1-6 alkyl, aminocarbonyl, C1-6 alkylcarbonyl optionally substituted with an aromatic heterocyclic group, arylcarbonyl, aryl C1-6 alkylcarbonyl, carboxy C1-6 alkylcarbonyl, carboxyarylcarbonyl, amino, C1-6 alkylcarbonylamino, C1-6 alkyl, C1-6 hydroxyalkyl, aryl, aryl C1-6 alkyl, C3-7 cycloalkyl, optionally substituted C4-7 cycloalkenyl, optionally substituted C4-7 azacycloalkyl, optionally substituted C4-7 diazacycloalkyl, optionally substituted C4-7 oxazacycloalkyl, optionally substituted C4-7 thiazacycloalkyl, optionally substituted C4-7 thiazacycloalkenyl, C3-7 cycloalkylalkyl, hydroxy C1-6 alkoxy C1-6 alkyl, C1-6 alkoxy C1-6 alkyl, di C1-6 alkylaminocarbonyl, di C1-6 alkylamino C1-6 alkylcarbonyl, optionally substituted C4-7 azacycloalkyl C1-6 alkylcarbonyl, optionally substituted C4-7 diazacycloalkyl C1-6 alkylcarbonyl, optionally substituted C4-7 oxazacycloalkyl C1-6 alkylcarbonyl, optionally substituted carboxamidine, C1-6 alkylaminothiocarbonyl, optionally substituted nitrovinyl, aminosulphonyl, di C1-6 alkylaminosulphonyl, or an optionally substituted spiroheterocyclic ring; wherein, unless otherwise defined optionally substituted means substituted with up to three substituents selected from the list consisting of: amino, alkylamino, alkyl, aryl, heterocyclyl, alkylaryl, aralkyl, oxo, hydroxy, nitrile.

Preferred optional substituents for the N-linked single or fused heterocyclic groups include isopropyl, 1-piperidinyl, (4-hydroxy)-1-piperidinyl.

When present oxo substituents are preferably alpha to the point of linkage of the N-linked single or fused heterocyclic group.

When a hetero atom of the N-linked single or fused heterocyclic group is substituted, preferred substituents are selected from C1-6 alkyl.

Fused heterocyclic groups include groups having one or more rings which share one or more atoms, such as spiro fused rings, or one or more bonds.

A suitable N-linked single ring heterocyclic group comprising a 5- membered saturated heterocyclic ring is a pyrrolidin -1- yl group.

A suitable N-linked single ring heterocyclic group comprising a 6- membered saturated heterocyclic ring is an optionally substituted piperidin-1-yl group, for example a 4-(piperidin-1-yl)piperidin-1-yl group or 4-aminopiperidin-1-yl group.

A suitable N-linked single ring 6- membered saturated heterocyclic group comprising an additional heteroatom is a morpholine or an optionally substituted piperazin-1yl group, for example an optionally substituted 4-alkylpiperazin-1-yl group.

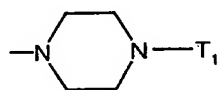
A suitable N-linked fused ring heterocyclic group includes a 5-or 6- membered saturated or unsaturated heterocyclic ring fused to a benzene ring.

A suitable N-linked fused ring heterocyclic group comprising a 6-membered saturated heterocyclic ring fused to a benzene ring is a 2-(1,2,3,4-tetrahydro)isoquinolinyl group.

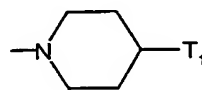
Suitable, N-linked fused heterocyclic groups include spiro fused groups, for example 1,4-dioxo-8-azaspiro[4.5]dec-8-yl group or 3-oxo-2,8-diazaspiro[4.5]dec-8-yl or 2,4-dioxo-1,3,8-triazaspiro[4.5]dec-8-yl or 2,7-diazaspiro[4.4]non-2-yl or 2,3-dioxo-1,8-diazaspiro[4.5]dec-8-yl.

One preferred value of  $-NY_1Y_2$  is a morpholine group or a piperidin-1-yl group or a piperazin-1-yl group which piperidinyl or piperazinyl group may be substituted or unsubstituted

A particularly preferred value of  $-NY_1Y_2$  is a group of formula (a) or (b):



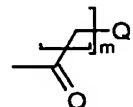
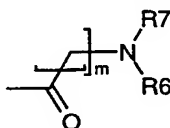
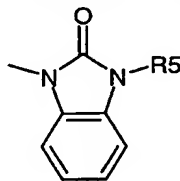
(a)



(b)

wherein  $T_1$  represents isopropyl, 1-piperidinyl or (4-hydroxy)-1-piperidinyl.

Suitably  $T_1$  represents one of the following groups:



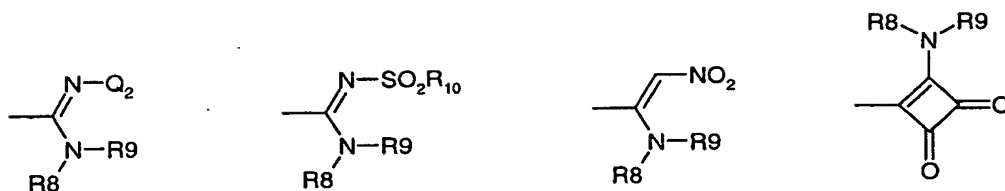
wherein  $R_5$  represents hydrogen or a lower alkyl, preferably hydrogen or methyl,  $m$  is an integer from 1 to 5 and  $R_6$  and  $R_7$  represent a lower alkyl, preferably methyl or ethyl or together form a heterocycle, for example a piperidine, morpholine or optionally substituted piperazine.

$Q_1$  represents 2-phthalic acid, a saturated or unsaturated C1-6 carboxylic acid or a heterocycle for example 2-imidazolyl or thiazolyl.

In a group of formula (a), suitably  $T_1$  represents also a heterocycle for example imidazolyl, thiazolyl, pyridyl, pyrimidyl, tetrazolyl or  $T_1$  represents an optionally substituted carboxamidine or a corresponding quaternary carboxamidine derivative.

In a group of formula (a) suitable  $T_1$  represents also one of the chemical entities below:





wherein  $R_8$  and  $R_9$  represent hydrogen, alkyl or together form a 5 to 7 membered ring with the N atom to which they are attached, preferably a pyrrolidin or piperidin ring and  $R_{10}$  represents  $C_{1-6}$  linear or branched alkyl or optionally substituted aryl

wherein  $Q_2$  is hydrogen, alkyl, aralkyl, aryl, cyano.

In a group of formula (a) suitable T1 represents also a sulphonamide of formula:



wherein  $R_{11}$  and  $R_{12}$  are independently selected from hydrogen;  $C_{1-6}$  alkyl; optionally substituted aryl or  $R_{11}$  and  $R_{12}$  together with the nitrogen atom to which they are attached represent an optionally substituted N-linked single or fused ring heterocyclic group.

In one particular aspect  $-NY_1Y_2$  is a moiety of formula (a).

In one particular aspect  $-NY_1Y_2$  is a moiety of formula (b).

Suitably,  $n$  is an integer from 1 to 6, favourably 1 to 4 and most preferably 1, 2 or 3.

Favourably,  $n$  represents 1.

Favourably,  $n$  represents 2.

Favourably,  $n$  represents 3.

Preferred compounds of formula (I) are those wherein:

$R$  is methyl, ethyl, isopropyl, or ter-butyl,  $R_1$  is hydrogen, methoxy or hydroxy,  $R_2$  is a moiety  $(CH_2)_n$  wherein  $n$  is 1, 2 or 3,  $R_3$  is phenyl and  $R_4$  is hydrogen, methyl or ethyl or  $R_4$  and  $R$  together with the carbon atom to which they are attached form an optionally substituted  $C_{3-12}$  cycloalkyl group and  $NY_1Y_2$  is:

(i) an optionally substituted piperazinyl group, especially a moiety of the above defined formula (a);

(ii) an optionally substituted piperidinyl group, especially a moiety of the above defined formula (b).

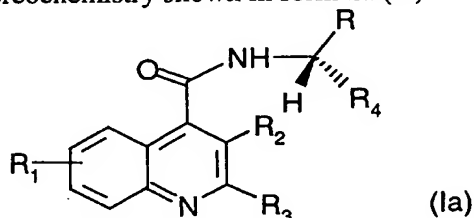
Further preferred compounds of formula (I) are those wherein:  $R$  is iso-propyl or ter-butyl,  $R_1$  is hydrogen,  $R_2$  is a moiety  $-(CH_2)_n-NY_1Y_2$  wherein  $n$  is 1,  $R_3$  is phenyl and  $R_4$  is methyl or  $R_4$  and  $R$  together with the carbon atom to which they are attached form a 2-adamantyl, a bicyclo[2.2.1]heptan-2-yl, indan-1-yl, indan-2-yl or a 1, 2, 3, 4-tetrahydronaphthalen-1-yl groups and  $NY_1Y_2$  is:

(i) a 4-isopropylpiperazin-1-yl group, especially a moiety of the above defined formula (a);

(ii) an optionally substituted 1-(piperidin-1-yl)piperidin-1-yl group of the above defined formula (b);

In particular should be mentioned the compounds of examples 1, 6, 7, 8, 9, and 10.

The compounds of formula (I) may have at least one asymmetric centre - for example the carbon atom labelled with an asterisk (\*) in the compound of formula (I) - and therefore may exist in more than one stereoisomeric form. The invention extends to all such stereoisomeric forms and to mixtures thereof, including racemates. In particular, the invention includes compounds wherein the asterisked carbon atom in formula (I) has the stereochemistry shown in formula (Ia):



wherein R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> are as defined in relation to formula (I).

The compounds of formula (I) or their salts or solvates are preferably in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, inter alia, having a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels.

A substantially pure form will generally contain at least 50% (excluding normal pharmaceutical additives), preferably 75%, more preferably 90% and still more preferably 95% of the compound of formula (I) or its salt or solvate.

One preferred pharmaceutically acceptable form is the crystalline form, including such form in pharmaceutical composition. In the case of salts and solvates the additional ionic and solvent moieties must also be non-toxic.

Suitable salts are pharmaceutically acceptable salts.

Suitable pharmaceutically acceptable salts include the acid addition salts with the conventional pharmaceutical acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric, succinic, benzoic, ascorbic and methanesulphonic.

Suitable pharmaceutically acceptable salts include salts of acidic moieties of the compounds of formula (I) when they are present, for example salts of carboxy groups or phenolic hydroxy groups.

Suitable salts of acidic moieties include metal salts, such as for example aluminium, alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl- $\beta$ -phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine, quinine or quinoline.

Suitable solvates are pharmaceutically acceptable solvates.

Suitable pharmaceutically acceptable solvates include hydrates.

The term 'alkyl' (unless specified to the contrary) when used alone or when forming part of other groups (such as the 'alkoxy' group) includes straight- or branched-chain alkyl groups containing 1 to 12 carbon atoms, suitably 1 to 6 carbon atoms, examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or tert-butyl group.

The term 'carbocyclic' refers to cycloalkyl and aryl rings.

The term 'cycloalkyl' includes groups having 3 to 12, suitably 4 to 6 ring carbon atoms.

The term 'aryl' includes phenyl and naphthyl, preferably phenyl which unless specified to the contrary optionally comprise up to five, preferably up to three substituents selected from halogen, alkyl, phenyl, alkoxy, haloalkyl, hydroxyalkyl, hydroxy, amino, nitro, cyano, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, or alkylcarbonyl groups.

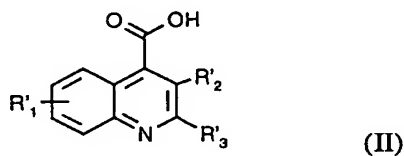
The term 'aromatic heterocyclic group' includes groups comprising aromatic heterocyclic rings containing from 5 to 12 ring atoms, suitably 5 or 6, and comprising up to four hetero-atoms in the or each ring selected from S, O or N.

Unless specified to the contrary, suitable substituents for any heterocyclic group includes up to 4 substituents selected from the group consisting of: alkyl, alkoxy, aryl and halogen or any two substituents on adjacent carbon atoms, together with the carbon atoms to which they are attached, may form an aryl group, preferably a benzene ring, and wherein the carbon atoms of the aryl group represented by the said two substituents may themselves be substituted or unsubstituted.

When used herein the term "halogen" refers to fluorine, chlorine, bromine and iodine, preferably fluorine, chlorine or bromine.

When used herein the term "acyl" includes residues of acids, in particular a residue of a carboxylic acid such as an alkyl- or aryl- carbonyl group.

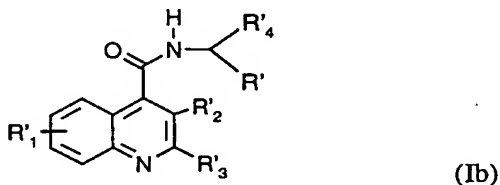
The invention also provides a process for the preparation of a compound of formula (I), or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (II) or an active derivative thereof:



wherein R'1, R'2 and R'3 are R1, R2 and R3 respectively as defined in relation to formula (I) or a group convertible to R1, R2 and R3 respectively; with a compound of formula (III):



wherein R' and R'4 are R and R4 as defined for formula (I) or a group or atom convertible to R and R4 respectively; to form a compound of formula (Ib):



wherein R', R'1, R'2, R'3 and R'4 are as defined above, and thereafter carrying out one or more of the following optional steps:

- (i) converting any one of R', R'1, R'2, R'3 and R'4 to R, R1, R2, R3 or R4 respectively as required, to obtain a compound of formula (I);
- (ii) converting a compound of formula (I) into another compound of formula (I); and
- (iii) preparing a salt of the compound of formula (I) and/or a solvate thereof.

Suitable groups convertible into other groups include protected forms of said groups.

Suitably R', R'1, R'2, R'3 or R'4 each represents R, R1, R2, R3 or R4 respectively or a protected form thereof.

It is favoured if the compound of formula (II) is present as an active derivative.

A suitable active derivative of a compound of formula (II) is a transient activated form of the compound of formula (II) or a derivative wherein the carboxy

group of the compound of formula (II) has been replaced by a different group or atom, for example by an acyl halide, preferably a chloride, or an acylazide or a carboxylic acid anhydride.

Other suitable active derivatives include: a mixed anhydride formed between the carboxyl moiety of the compound of formula (II) and an alkyl chloroformate; an activated ester, such as a cyanomethyl ester, thiophenyl ester, p-nitrophenyl ester, p-nitrothiophenyl ester, 2,4,6-trichlorophenyl ester, pentachlorophenyl ester, pentafluorophenyl ester, N-hydroxy-phtalimido ester, N-hydroxypiperidine ester, N-hydroxysuccinimide ester, N-hydroxy benzotriazole ester; alternatively, the carboxy group of the compound of formula (II) may be activated using a carbodiimide or N,N'-carbonyldiimidazole.

The reaction between the compound of formula (II) or the active derivative thereof and the compound of formula (III) is carried out under the appropriate conventional conditions for the particular compounds chosen. Generally, when the compound of formula (II) is present as an active derivative the reaction is carried out using the same solvent and conditions as used to prepare the active derivative, preferably the active derivative is prepared *in situ* prior to forming the compound of formula (Ib) and thereafter the compound of formula (I) or a salt thereof and/or a solvate thereof is prepared.

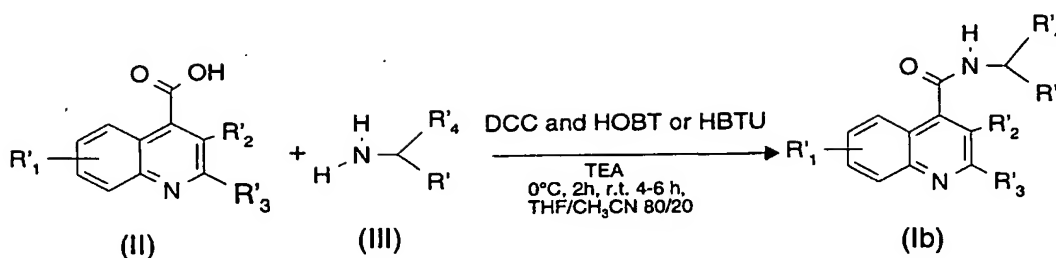
For example, the reaction between an active derivative of the compound of formula (II) and the compound of formula (III) may be carried out:

(a) by first preparing an acid chloride and then coupling said chloride with the compound of formula (III) in the presence of an inorganic or organic base in a suitable aprotic solvent such as dimethylformamide (DMF) at a temperature in a range from -70 to 50°C (preferably in a range from -10 to 20°C); or

(b) by treating the compound of formula (II) with a compound of formula (III) in the presence of a suitable condensing agent, such as for example N,N'-carbonyldiimidazole (CDI) or a carbodiimide such as dicyclohexylcarbodiimide (DCC) or N-dimethylaminopropyl-N'-ethylcarbodiimide, preferably in the presence of N-hydroxybenzotriazole (HOBT) to maximise yields and avoid racemization processes (see *Synthesis*, 453, 1972) or O-benzotriazol-1-yl-N,N,N',N'-tetramethyluroniumhexafluorophosphate (HBTU), in an aprotic solvent, such as a mixture of acetonitrile (MeCN) and tetrahydrofuran (THF), for example a mixture in a volume ratio of from 1:9 to 7:3 (MeCN:THF), at any temperature providing a suitable rate of formation of the required product, such as a temperature in the range of from -70 to 50°C, preferably in a range of from -10 to 25°C, for example at 0°C.

A preferred reaction is set out in Scheme 1 shown below:

#### Scheme 1



wherein  $R'$ ,  $R'_1$ ,  $R'_2$ ,  $R'_3$  and  $R'_4$  are as defined above.

It will be appreciated that a compound of formula (Ib) may be converted to a compound of formula (I), or one compound of formula (I) may be converted to another compound of formula (I) by interconversion of suitable substituents. Thus, certain compounds of formula (I) and (Ib) are useful intermediates in forming other compounds of the present invention.

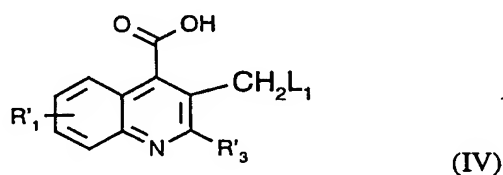
Accordingly, in a further aspect the invention provides a process for preparing a compound of formula (I), or a salt thereof and/or a solvate thereof, which process comprises converting a compound of the above defined formula (Ib) wherein at least one of  $R'$ ,  $R'_1$ ,  $R'_2$ ,  $R'_3$  or  $R'_4$  is not  $R$ ,  $R_1$ ,  $R_2$ ,  $R_3$  or  $R_4$  respectively, thereby to provide a compound of formula (I); and thereafter, as required, carrying out one or more of the following optional steps:

- (i) converting a compound of formula (I) into another compound of formula (I); and
- (ii) preparing a salt of the compound of formula (I) and/or a solvate thereof.

Suitably, in the compound of formula (Ib) the variables  $R'$ ,  $R'_1$ ,  $R'_2$ ,  $R'_3$  and  $R'_4$  are  $R$ ,  $R_1$ ,  $R_2$ ,  $R_3$  or  $R_4$  respectively or they are protected forms thereof.

The above mentioned conversions, protections and deprotections are carried out using the appropriate conventional reagents and conditions and are further discussed below.

A compound of formula (II) or the corresponding alkyl (such as methyl or ethyl) ester wherein  $n$  is an integer 1, is prepared by reacting a compound of formula (IV) or the corresponding alkyl (such as methyl or ethyl) ester:



wherein  $R'_1$  and  $R'_3$  are as defined above and  $L_1$  represents a halogen atom such as a bromine atom, with a compound of formula (V):

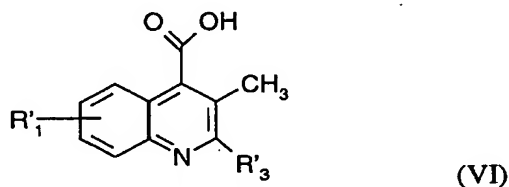


wherein  $\text{Y}'_1$  and  $\text{Y}'_2$  are respectively  $\text{Y}_1$  and  $\text{Y}_2$  as defined in relation to formula (I) or protected forms thereof.

Suitably,  $\text{Y}'_1$  and  $\text{Y}'_2$  are  $\text{Y}_1$  and  $\text{Y}_2$ .

Suitably, reaction between the compounds of formulae (IV) or the corresponding alkyl (such as methyl or ethyl) ester and (V) is carried out under conventional amination conditions, for example when  $\text{L}_1$  is a bromine atom then the reaction is conveniently carried out in an aprotic solvent, such as tetrahydrofuran or dimethylformamide at any temperature providing a suitable rate of formation of the required product, usually at ambient temperature; preferably the reaction is carried out in the presence of triethylamine (TEA) or potassium carbonate ( $\text{K}_2\text{CO}_3$ ).

A compound of formula (IV) or the corresponding alkyl (such as methyl or ethyl) ester is prepared by appropriate halogenation of a compound of formula (VI) or the corresponding alkyl (such as methyl or ethyl) ester:



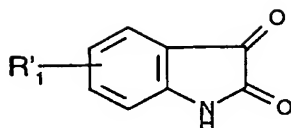
wherein  $\text{R}'_1$  and  $\text{R}'_3$  are as defined above in relation to formula (II).

Suitable halogenation reagents are conventional reagents depending upon the nature of the halogen atom required, for example when  $\text{L}_1$  is bromine a preferred halogenation reagent is N-bromosuccinimide (NBS).

The halogenation of the compound of formula (VI) or the corresponding alkyl (such as methyl or ethyl) ester is carried out under conventional conditions, for example bromination is carried out by treatment with NBS in an inert solvent, such as 1,2-dichloroethane or  $\text{CH}_3\text{CN}$ , at any temperature providing a suitable rate of formation of the required product, suitably at an elevated temperature such as a temperature in the range of  $60^\circ\text{C}$  to  $100^\circ\text{C}$ , for example  $80^\circ\text{C}$ ; preferably the reaction is carried out in the presence of a catalytic amount of benzoyl peroxide.

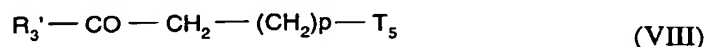
In the case in which the corresponding alkyl (such as methyl or ethyl) ester of compounds (VI), (IV) and (II) are utilised, an hydrolysis to compound (II) is required before conversion to compound (Ib) in Scheme 1. Such hydrolysis can be carried out under acidic conditions, such 10-36% hydrochloric acid at a temperature in the range between  $30$  and  $100^\circ\text{C}$ .

A compound of formula (II) wherein  $\text{R}'_2$  represents  $-(\text{CH}_2)_2\text{-g-NY}_1\text{Y}_2$ , is conveniently prepared by reacting a compound of formula (VII):



(VII)

wherein  $R'_1$  is as defined in relation to formula (II), with a compound of formula (VIII):



wherein  $R'_3$  is as defined in relation to formula (II), and  $T_5$  is a group  $-NY_1Y_2$  as defined in relation to formula (I) or a protected form thereof or a group convertible thereto, and  $p$  is an integer in the range of 2 to 9; and thereafter as required removing any protecting group and/or converting any group  $T_5$  to  $NY_1Y_2$ .

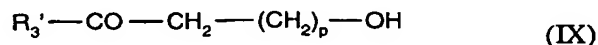
The reaction between the compounds of formula (VII) and (VIII) is conveniently carried out using Pfitzinger reaction conditions (see for example J. Prakt. Chem. 33, 100 (1886), J. Prakt. Chem. 38, 582 (1888), J. Chem. Soc. 106 (1948) and Chem. Rev. 35, 152 (1944)), for example in an alkanolic solvent such as ethanol, at any temperature providing a suitable rate of formation of the required product, but generally at an elevated temperature, such as the reflux temperature of the solvent, and preferably in the presence of a base such as potassium hydroxide or potassium tert-butoxide.

Protected forms of  $-NY_1Y_2$  will vary according to the particular nature of the group being protected but will be chosen in accordance with normal chemical practice.

Groups convertible to  $-NY_1Y_2$  include groups dictated by conventional chemical practice to be required and to be appropriate, depending upon the specific nature of the  $-NY_1Y_2$  consideration.

Suitable deprotection methods for deprotecting protected forms of  $NY_1Y_2$  and conversion methods for converting  $T_5$  to  $NY_1Y_2$  will be those used conventionally in the art depending upon the particular groups under consideration with reference to standard texts such as Greene, T.W. and Wuts, P.G.M. Protective Groups in Organic Synthesis, John Wiley & Sons Inc. New York, 1991 (Second Ed.) or in Kocienski, P.J. Protecting groups. George Thieme Verlag, New York, 1994. Chemistry of the Amino Group, Patai (Ed.), Interscience, New York 1968; Advanced Organic Chemistry, March J, John Wiley & Sons, New York, 1992.

A compound of formula (VIII) is prepared from a compound of formula (IX):





wherein  $R'_3$  is as defined in relation to formula (II) and  $p$  is as defined in relation to formula (VIII), by first halogenating, preferably brominating, or mesylating the compound of formula (IX) and thereafter reacting the halogenation or mesylation product so formed with a compound capable of forming a group  $T_5$  so as to provide the required compound of formula (VII).

In the above mentioned conversion of a compound of formula (IX) to a compound of formula (VIII), where  $T_5$  is a group  $-NY_1Y_2$ , a compound capable of forming a group  $T_5$ , is a compound of the above defined formula (V).

The halogenation of the compound of formula (IX) is suitably carried out using a conventional halogenation reagent. Mesylation is conveniently carried out using mesyl chloride in an inert solvent such as methylene dichloride, at a temperature below room temperature, such as  $0^\circ\text{C}$ , preferably in the presence of triethylamine.

The reaction conditions between the compound of formula (IX) and the compound capable of forming a group  $T_5$  will be those conventional conditions dictated by the specific nature of the reactants, for example when the  $T_5$  required is a group  $NY_1Y_2$  and the required compound capable of forming a group  $T_5$  is a compound of the above defined formula (V), then the reaction between the halogenation or mesylation product of the compound of formula (IX) and the compound of formula (V) is carried out under analogous conditions to those described for the reaction between the compounds of formulae (IV) and (V).

Other compounds capable of forming a group  $T_5$  will depend upon the particular nature of  $T_5$ , but will be those appropriate compounds dictated by conventional chemical practice with reference to standard texts such as Chemistry of the Amino Group, Patai (Ed.), Interscience, New York 1968; Advanced Organic Chemistry, March J, John Wiley & Sons, New York, 1992.

A compound of formula (IX) may be prepared by reacting a compound of formula (X):



wherein  $p$  is as defined in relation to formula (VIII), with a lithium salt of formula (XI):



wherein  $R'_3$  is as defined in relation to formula (II).

The reaction between the compounds of formulae (X) and (XI) can be carried out in an aprotic solvent, such as diethyl-ether at any temperature providing a suitable rate of formation of the required product, usually at a low temperature such as in the range of  $-10^\circ\text{C}$  to  $-30^\circ\text{C}$ , for example  $-20^\circ\text{C}$ .

The compounds of formula (III) are known commercially available compounds or they can be prepared from known compounds by known methods, or methods analogous to those used to prepare known compounds, for example the methods described in Liebigs Ann. der Chemie (1936), 523, 199.

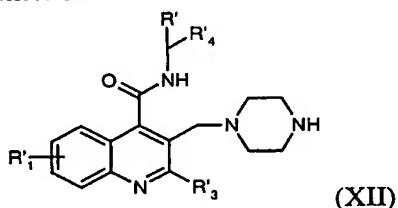
Chiral compounds of formula (III) wherein R and R<sub>4</sub> are alkylare described in J. Org. Chem. (1996), 61 (12), 4130-4135.

The compounds of formula (V) are known, commercially available compounds or they can be prepared using methods analogous to those used to prepare known compounds; for example the methods described in the Chemistry of the Amino Group, Patai (Ed.), Interscience, New York 1968 or Advanced Organic Chemistry, March J, John Wiley & Sons, New York, 1992. J. Heterocyclic Chem. (1990), 27, 1559; Synthesis (1975), 135, Bioorg. Med. Chem. Lett. (1997), 7, 555, or Protective Groups in Organic Synthesis (second edition), Wiley Interscience, (1991). or J. Org. Chem. (1990), 55 (8), 2552-4 or ibid. (1995), 60 (15), 4928-9.

The compounds of formula (VII) are known compounds or they are prepared according to methods used to prepare known compounds for example those disclosed in J. Org. Chem. 21, 171 (1955); J. Org. Chem. 21, 169 (1955).

The compounds of formula (X) and (XI) are known compounds or they are prepared according to methods used to prepare known compounds for example those disclosed by Krow G. R. in Organic Reactions, Vol 43, page 251, John Wiley & Sons Inc.1994 (for the compounds of formula (X)) and Organometallics in Synthesis, Schlosser M.(Ed), John Wiley & Sons Inc.1994 (for the compounds of formula (XI))

Compounds of formula (I) wherein R<sub>2</sub> represents a moiety  $-(CH_2)_n-NY_1Y_2$  and  $-NY_1Y_2$  is a piperazinyl group of formula (a) can alternatively be prepared by reacting a compound of formula XII

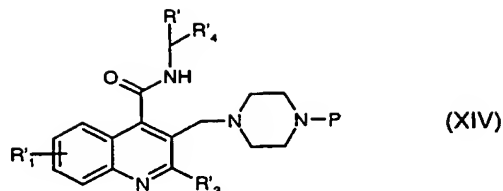


wherein R', R'<sub>1</sub>, R'<sub>3</sub> and R'<sub>4</sub> are as defined above with a compound of formula (XIII)



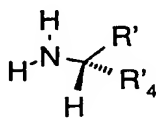
wherein T1 is as defined above and L2 represents a leaving group such as, for example, halogen, mesylate, -SAlkyl -OAlkyl.

Compounds of formula (XII) are prepared by removing the protective group of a compound of formula (XIV)

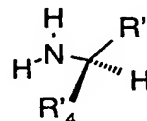


wherein R', R'1, R'3 and R'4 are as defined above and P is an amine protective group, for example fmoc or benzyl, preferably fmoc. The protective group is removed by standard methods described in the literature, for example the fmoc residue is splitted by action of piperidine at room temperature in a solvent like acetonitrile.

As hereinbefore mentioned, the compounds of formula (I) may exist in more than one stereoisomeric form - and the process of the invention may produce racemates as well as enantiomerically pure forms. Accordingly, a pure enantiomer of a compound of formula (I) is obtained by reacting a compound of the above defined formula (II) with an appropriate enantiomerically pure primary amine of formula (IIIa) or (IIIc):

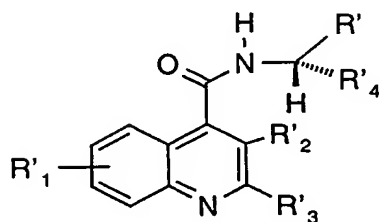


(IIIa)

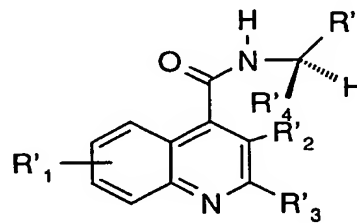


(IIIc)

wherein R' and R'4 are as defined above, to obtain a compound of formula (I'a) or (I'c):



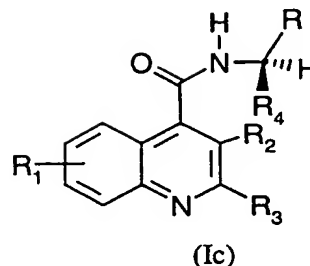
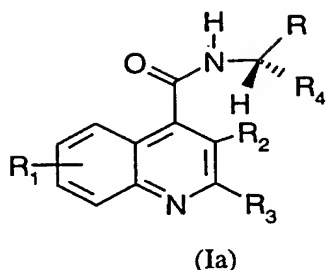
(I'a)



(I'c)

wherein R', R'1, R'2, R'3 and R'4 are as defined above.

Compounds of formula (I'a) or (I'c) may subsequently be converted to compounds of formula (Ia) or (Ic) by the methods of conversion mentioned before:



wherein R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are as defined above.

An alternative method for separating optical isomers is to use conventional, fractional separation methods in particular fractional crystallization methods. Thus, a pure enantiomer of a compound of formula (I) is obtained by fractional crystallisation of a diastereomeric salt formed by reaction of the racemic compound of formula (I) with an optically active strong acid resolving agent, such as camphosulphonic acid, in an appropriate alcoholic solvent, such as ethanol or methanol, or in a ketonic solvent, such as acetone. The salt formation process should be conducted at a temperature between 20°C and 80°C, preferably at 50°C.

In the case in which other basic functionalities, such as primary, secondary or tertiary amine, are present in the molecule, a wider range of optically active acid resolving agents become available, including tartaric acid, O,O'-di-p-toluoyletartaric acid and mandelic acid.

A suitable conversion of one compound of formula (I) into a further compound of formula (I) involves converting one group R<sub>1</sub> into another group R<sub>2</sub> by for example:

- (i) converting a ketal into a ketone, by such as mild acidic hydrolysis, using for example dilute hydrochloric acid;
- (ii) reducing a ketone to a hydroxyl group by use of a borohydride reducing agent;
- (iii) converting a carboxylic ester group into a carboxyl group using basic hydrolysis; and/or
- (iv) reducing a carboxylic ester group to a hydroxymethyl group, by use of a borohydride reducing agent.

As indicated above, where necessary, the conversion of any group R', R'<sub>1</sub>, R'<sub>2</sub>, R'<sub>3</sub> and R'<sub>4</sub> into R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> or R<sub>4</sub> which as stated above are usually protected forms of R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> or R<sub>4</sub> may be carried out using appropriate conventional conditions such as the appropriate deprotection procedure.

It will be appreciated that in any of the above mentioned reactions any reactive group in the substrate molecule may be protected and deprotected according to conventional chemical practice, for example as described by Greene, T.W. and Wuts, P.G.M. *Protective Groups in Organic Synthesis*, John Wiley & Sons Inc. New York,

1991 (Second Edt.) or in Kocienski, P.J. Protecting groups. George Thieme Verlag, New York, 1994.

Suitable protecting groups in any of the above mentioned reactions are those used conventionally in the art. Thus, for example suitable hydroxyl protecting groups include benzyl or trialkylsilyl groups.

The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected. Thus for example a benzyloxy group may be prepared by treatment of the appropriate compound with a benzyl halide, such as benzyl bromide, and thereafter, if required, the benzyl group may be conveniently removed using catalytic hydrogenation or a mild ether cleavage reagent such as trimethylsilyl iodide or boron tribromide.

As indicated above, the compounds of formula (I) have useful pharmaceutical properties.

Accordingly the present invention also provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use as an active therapeutic substance.

In particular, the present invention also provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the treatment or prophylaxis of the Primary and Secondary Conditions.

Preferred Primary Conditions are the NK-2 Conditions

The present invention further provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of the Primary and Secondary Conditions.

As mentioned above the Primary conditions include respiratory diseases, such as chronic obstructive pulmonary disease (COPD), asthma, airway hyperreactivity, cough; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis, rheumatoid arthritis and inflammatory pain; neurogenic inflammation or peripheral neuropathy, allergies such as eczema and rhinitis; ophthalmic diseases such as ocular inflammation, conjunctivitis, vernal conjunctivitis and the like; cutaneous diseases, skin disorders and itch, such as cutaneous wheal and flare, contact dermatitis, atopic dermatitis, urticaria and other eczematoid dermatitis; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosus; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as

ulcerative colitis, Crohn's disease, irritable bowel syndrome (IBS), gastro-exophageous reflex disease (GERD); urinary incontinence and disorders of the bladder function; renal disorders.

As mentioned above, the Secondary conditions disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; neurodegenerative disorders such as AIDS related dementia, senile dementia of the Alzheimer type, Alzheimer's disease, Down's syndrome, Huntington's disease, Parkinson's disease, movement disorders and convulsive disorders (for example epilepsy); demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis and other neuropathological disorders such as diabetic neuropathy, AIDS related neuropathy, chemotherapy-induced neuropathy and neuralgia; addiction disorders such as alcoholism; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; eating disorders (such as food intake disease); fibrosing and collagen diseases such as scleroderma and eosinophilic fasciitis; disorders of the blood flow caused by vasodilation and vasospastic diseases such as angina, migraine and Reynaud's disease and pain or nociception, for example, that is attributable to or associated with any of the foregoing conditions especially the transmission of pain in migraine.

Such a medicament, and a composition of this invention, may be prepared by admixture of a compound of the invention with an appropriate carrier. It may contain a diluent, binder, filler, disintegrant, flavouring agent, colouring agent, lubricant or preservative in conventional manner.

These conventional excipients may be employed for example as in the preparation of compositions of known agents for treating the conditions.

Preferably, a pharmaceutical composition of the invention is in unit dosage form and in a form adapted for use in the medical or veterinarial fields. For example, such preparations may be in a pack form accompanied by written or printed instructions for use as an agent in the treatment of the conditions.

The suitable dosage range for the compounds of the invention depends on the compound to be employed and on the condition of the patient. It will also depend, inter alia, upon the relation of potency to absorbability and the frequency and route of administration.

The compound or composition of the invention may be formulated for administration by any route, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may be designed to give slow release of the active ingredient.

Compositions may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

The compositions, for example those suitable for oral administration, may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinyl-pyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable setting agents such as sodium lauryl sulphate.

Solid compositions may be obtained by conventional methods of blending, filling, tableting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. When the composition is in the form of a tablet, powder, or lozenge, any carrier suitable for formulating solid pharmaceutical compositions may be used, examples being magnesium stearate, starch, glucose, lactose, sucrose, rice flour and chalk. Tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating. The composition may also be in the form of an ingestible capsule, for example of gelatin containing the compound, if desired with a carrier or other excipients.

Compositions for oral administration as liquids may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; aqueous or non-aqueous vehicles, which include edible oils, for example almond oil, fractionated coconut oil, oily esters, for example esters of glycerine, or propylene glycol, or ethyl alcohol, glycerine, water or normal saline; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

The compounds of this invention may also be administered by a non-oral route. In accordance with routine pharmaceutical procedure, the compositions may be formulated, for example for rectal administration as a suppository. They may also be formulated for presentation in an injectable form in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable liquid, e.g. sterile pyrogen-free water or a parenterally acceptable oil or a mixture of liquids. The liquid

may contain bacteriostatic agents, anti-oxidants or other preservatives, buffers or solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives. Such forms will be presented in unit dose form such as ampoules or disposable injection devices or in multi-dose forms such as a bottle from which the appropriate dose may be withdrawn or a solid form or concentrate which can be used to prepare an injectable formulation.

The compounds of this invention may also be administered by inhalation, via the nasal or oral routes. Such administration can be carried out with a spray formulation comprising a compound of the invention and a suitable carrier, optionally suspended in, for example, a hydrocarbon propellant.

Preferred spray formulations comprise micronised compound particles in combination with a surfactant, solvent or a dispersing agent to prevent the sedimentation of suspended particles. Preferably, the compound particle size is from about 2 to 10 microns.

A further mode of administration of the compounds of the invention comprises transdermal delivery utilising a skin-patch formulation. A preferred formulation comprises a compound of the invention dispersed in a pressure sensitive adhesive which adheres to the skin, thereby permitting the compound to diffuse from the adhesive through the skin for delivery to the patient. For a constant rate of percutaneous absorption, pressure sensitive adhesives known in the art such as natural rubber or silicone can be used.

As mentioned above, the effective dose of compound depends on the particular compound employed, the condition of the patient and on the frequency and route of administration. A unit dose will generally contain from 20 to 1000 mg and preferably will contain from 30 to 500 mg, in particular 50, 100, 150, 200, 250, 300, 350, 400, 450, or 500 mg. The composition may be administered once or more times a day for example 2, 3 or 4 times daily, and the total daily dose for a 70 kg adult will normally be in the range 100 to 3000 mg. Alternatively the unit dose will contain from 2 to 20 mg of active ingredient and be administered in multiples, if desired, to give the preceding daily dose.

No unacceptable toxicological effects are expected with compounds of the invention when administered in accordance with the invention.

The present invention also provides a method for the treatment and/or prophylaxis of the Primary and Secondary Conditions in mammals, particularly humans, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective, non-toxic pharmaceutically acceptable amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.



The activity of the compounds of the present invention, as NK<sub>3</sub> ligands, is determined by their ability to inhibit the binding of the radiolabelled NK<sub>3</sub> ligands, [<sup>125</sup>I]-[Me-Phe<sup>7</sup>]-NKB or [<sup>3</sup>H]-Senktide, to guinea-pig and human NK<sub>3</sub> receptors (Renzetti et al, 1991, *Neuropeptide*, 18, 104-114; Buell et al, 1992, *FEBS*, 299(1), 90-95; Chung et al, 1994, *Biochem. Biophys. Res. Commun.*, 198(3), 967-972).

The binding assays utilized allow the determination of the concentration of the individual compound required to reduce by 50% the [<sup>125</sup>I]-[Me-Phe<sup>7</sup>]-NKB and [<sup>3</sup>H]-Senktide specific binding to NK<sub>3</sub> receptor in equilibrium conditions (IC<sub>50</sub>).

Binding assays provide for each compound tested a mean IC<sub>50</sub> value of 2-5 separate experiments performed in duplicate or triplicate. The most potent compounds of the present invention show IC<sub>50</sub> values in the range 10-1000 nM. The NK<sub>3</sub>-antagonist activity of the compounds of the present invention is determined by their ability to inhibit senktide-induced contraction of the guinea-pig ileum (Maggi et al, 1990, *Br. J. Pharmacol.*, 101, 996-1000) and rabbit isolated iris sphincter muscle (Hall et al., 1991, *Eur. J. Pharmacol.*, 199, 9-14) and human NK<sub>3</sub> receptors-mediated Ca<sup>++</sup> mobilization (Mochizuki et al, 1994, *J. Biol. Chem.*, 269, 9651-9658). Guinea-pig and rabbit *in-vitro* functional assays provide for each compound tested a mean K<sub>B</sub> value of 3-8 separate experiments, where K<sub>B</sub> is the concentration of the individual compound required to produce a 2-fold rightward shift in the concentration-response curve of senktide. Human receptor functional assay allows the determination of the concentration of the individual compound required to reduce by 50% (IC<sub>50</sub> values) the Ca<sup>++</sup> mobilization induced by the agonist NKB. In this assay, the compounds of the present invention behave as antagonists.

The activity of the compounds of the present invention, as NK-2 ligands, is determined by their ability to inhibit the binding of the radiolabelled NK-2 ligands, [<sup>125</sup>I]-NKA or [<sup>3</sup>H]-NKA, to human NK-2 receptors (Aharony et al, 1992, *Neuropeptide*, 23, 121-130).

The binding assays utilized allow the determination of the concentration of the individual compound required to reduce by 50% the [<sup>125</sup>I]-NKA and [<sup>3</sup>H]-NKA specific binding to NK-2 receptor in equilibrium conditions (IC<sub>50</sub>).

Binding assays provide for each compound tested a mean IC<sub>50</sub> value of 2-5 separate experiments performed in duplicate or triplicate. The most potent compounds of the present invention show IC<sub>50</sub> values in the range 1-1000 nM, such as 1-100 nM. The NK-2-antagonist activity of the compounds of the present invention is determined by their ability to inhibit human NK-2 receptor-mediated Ca<sup>++</sup> mobilization (Mochizuki et al, 1994, *J. Biol. Chem.*, 269, 9651-9658). Human receptor functional assay allows the determination of the concentration of the individual compound required to reduce by 50% (IC<sub>50</sub> values) the Ca<sup>++</sup> mobilization

induced by the agonist NKA. In this assay, the compounds of the present invention behave as antagonists.

The therapeutic potential of the compounds of the present invention in treating the conditions can be assessed using rodent disease models.

As stated above, the compounds of formula (I) are also considered to be useful as diagnostic tool. Accordingly, the invention includes a compound of formula (I) for use as diagnostic tools for assessing the degree to which neurokinin-2 and neurokinin-3 receptor activity (normal, overactivity or underactivity) is implicated in a patient's symptoms. Such use comprises the use of a compound of formula (I) as an antagonist of said activity, for example including but not restricted to tachykinin agonist-induced inositol phosphate turnover or electrophysiological activation, of a cell sample obtained from a patient. Comparison of such activity in the presence or absence of a compound of formula (I), will disclose the degree of NK-2 and NK-3 receptor involvement in the mediation of agonist effects in that tissue.

The following Descriptions illustrate the preparation of the intermediates, whereas the following Examples illustrate the preparation of the compounds of the invention.

## Descriptions and Examples

**DESCRIPTION 1: 3-Methyl-2-phenyl-quinoline-4-carboxylic acid methyl ester**  
30 g (114 mmol) of 3-methyl-2-phenylquinoline-4-carboxylic acid (CAS [43071-45-0]) were suspended in 250 ml of dry  $\text{CH}_2\text{Cl}_2$ ; 20 ml (230 mmol) of oxalyl chloride dissolved in 120 ml of  $\text{CH}_2\text{Cl}_2$  were added dropwise and the reaction mixture was stirred at room temperature for 30 min. Two drops of DMF were added and the reaction was stirred for additional 30 min. The solvent was evaporated *in vacuo* to dryness, the residue was taken up with 100 ml of  $\text{CH}_2\text{Cl}_2$  and 100 ml of MeOH, dissolved in 400 ml of  $\text{CH}_2\text{Cl}_2$ , were added dropwise. After stirring for 18 h the solvent was evaporated *in vacuo* to dryness, the residue was taken up with  $\text{CH}_2\text{Cl}_2$  and washed with 1%  $\text{NaHCO}_3$ ; the organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and evaporated *in vacuo* to dryness to yield 31.6 g of the title compound as a solid, which was used in the following reaction without further purification.

$\text{C}_{18}\text{H}_{15}\text{NO}_2$

MW 277.31

MP = 73-75°C

IR (KBr) 3441, 3051, 2954, 1731, 1582, 1556  $\text{cm}^{-1}$ .

**DESCRIPTION 2 : 3-Bromomethyl-2-phenyl-quinoline-4-carboxylic acid methyl ester**

10 g (36 mmol) of 3-methyl-2-phenyl-quinoline-4-carboxylic acid methyl ester (compound of Description 1) were dissolved in 500 ml of  $\text{CH}_3\text{CN}$ ; 13 g (72 mmol) of N-bromosuccinimide were added and the reaction mixture was heated to reflux. After adding 1 g (4.1 mmol) of dibenzoylperoxide, the reaction was refluxed for 24 h; then additional 4 g (22.5 mmol) of N-bromosuccinimide and 0.5 g (2.0 mmol) of dibenzoylperoxide were added and the reaction was refluxed for 4 h. The solvent was evaporated *in vacuo* to dryness to yield 26.1 g of crude title compound which has been used in the following reaction without further purification.

$\text{C}_{18}\text{H}_{14}\text{BrNO}_2$

MW = 356.23

**DESCRIPTION 3: 3-(4-Isopropyl-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid methyl ester**

7.8 g of crude 3-bromomethyl-2-phenyl-quinoline-4-carboxylic acid methyl ester (compound of Description 2) were dissolved, under nitrogen atmosphere, in 130 ml of dry THF. The solution was cooled to 10 °C and 2.8 g (21.6 mmol) of 1-isopropyl-piperazine, dissolved in 20 ml of THF, were added dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. Salts were filtered off and the filtrate was evaporated *in vacuo* to dryness, taken up with 2 N HCl and

washed with EtOAc; the aqueous layer was basified with 10% NaOH and extracted with  $\text{CH}_2\text{Cl}_2$ . The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and evaporated *in vacuo* to dryness to obtain a crude material which was purified by flash column chromatography on 230-400 mesh silica gel, utilising a mixture of  $\text{Et}_2\text{O}/i\text{Pr}_2\text{O}$  70:30 containing 0.3 % ammonium hydroxide (28%). 3.8 g of the title compound were recovered as a yellow solid.

$\text{C}_{25}\text{H}_{29}\text{N}_3\text{O}_2$

MW = 403.54

IR: (KBr) 3441, 3065, 2946, 1731, 1580, 1555  $\text{cm}^{-1}$ .

**DESCRIPTION 4: 3-(4-Isopropyl-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid dihydrochloride**

3.8 g (9.42 mmol) of 3-(4-isopropyl-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid methyl ester (compound of Description 3) were dissolved in 100 ml of 6 N HCl and refluxed for 4 h. Evaporation to dryness afforded 4.0 g of crude title compound, which was used in the following reaction without further purification.

$\text{C}_{24}\text{H}_{27}\text{N}_3\text{O}_2 \cdot 2\text{HCl}$

MW = 389.50

MP = 177-180°C

IR: (KBr) 3408, 2928, 2666, 1716, 1632  $\text{cm}^{-1}$ .

**DESCRIPTION 5: 3-[1,4']Bipiperidinyl-1'-ylmethyl-2-phenyl-quinoline-4-carboxylic acid methyl ester**

5 g (14 mmol) of 3-bromomethyl-2-phenyl-quinoline-4-carboxylic acid methyl ester (compound of Description 2), 2.9 g, (15.4 mmol) of 90% [1,4']Bipiperidinyl (Aldrich), 2.7 ml (15.4 mmol) of ethyl-diisopropyl-amine were dissolved in 100 ml of dry THF and the mixture was stirred for one night at 50°C. The solvent was concentrated, the residue was dissolved in  $\text{CH}_2\text{Cl}_2$ , washed with water, and the organic phase was dried over  $\text{MgSO}_4$ . After concentration of the solvent, the residue was purified by flash chromatography over 160 g of silicagel (eluting with  $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}$  : 95/5/0.5) affording 3.5 g (yield 56%) of the title compound as a white solid.

$\text{C}_{28}\text{H}_{33}\text{N}_3\text{O}_2$

MW = 443.59

$^1\text{H-NMR}$   $\delta$  ( $\text{CDCl}_3$ ) : 1.29-2.02(12H); 2.25(1H); 2.47(4H); 2.78(2H); 3.66(2H); 4.05(3H); 7.38-7.55(5Har); 7.58(1Har); 7.72(1Har); 7.88(1Har); 8.17(1Har)ppm.

**DESCRIPTION 6 : 3-[1,4']Bipiperidinyl-1'-ylmethyl-2-phenyl-quinoline-4-carboxylic acid dihydrochloride**

3.5 g (7.9 mmol) of 3-[1,4']bipiperidinyl-1'-ylmethyl-2-phenyl-quinoline-4-carboxylic acid methyl ester (compound of Description 5) and 50 ml of 6N HCl are refluxed for

1.5 h and then concentrated to dryness. The residue was triturated in acetone. This process was re-applied twice to the solid thus obtained affording, after drying *in vacuo*, 4.5 g of the title compound as a crude dihydrochloride used without further purification in the next step.

$C_{27}H_{33}N_3O_2 \cdot 2HCl$

MW = 575.44

$^1H$ -NMR  $\delta$  (DMSO- $d_6$ ): 1.16-2.29(10H); 2.62-3.38(8H); 4.46(2H); 5.77(1H, exch with  $D_2O$ ); 7.45-8.30(9H, ar); 11.12 (1H, exch with  $D_2O$ ) ppm.

The following Examples illustrate the invention; Table 1 summarizes all the compounds of the Examples 1-12 and their analytical data; Table 2 describes NMR spectroscopic data of Examples 1-12 and Table 3 illustrates chemical names of compounds of Examples 1-12.

**EXAMPLE 1: 3-(4-Isopropyl-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((R,S)- 1,2-dimethyl-propyl)-amide dihydrochloride**

2.3 g (5.0 mmol) of crude 3-(4-isopropyl-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid dihydrochloride (compound of Description 4) were dissolved in 200 ml of a 1:1 mixture of  $CH_2Cl_2/CH_3CN$ ; 2.5 g (6.5 mmol) of O-benzotriazol-1-yl-N,N,N',N'-tetramethyluroniumhexafluorophosphate (HBTU) were added and the reaction mixture was cooled to 0 °C. 1.15 ml (10 mmol) of 1,2-dimethyl-propylamine, dissolved in 10 ml of dry  $CH_2Cl_2$ , were added dropwise and the reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated *in vacuo* to dryness and the residue was taken up with EtOAc and washed with  $H_2O$ , 1 N NaOH and brine, dried over  $Na_2SO_4$  and evaporated to dryness to yield a crude material which was purified by flash column chromatography on 230-400 mesh silica gel, utilising a mixture of  $CH_2Cl_2/MeOH$  95:5 containing 0.5 %  $NH_4OH$  (28%). The residue was dissolved in acetone and acidified with  $HCl/Et_2O$ ; the precipitate so formed was recovered by suction filtration to yield 0.3 g of title compound as a yellow solid.

$C_{29}H_{38}N_4O \cdot 2HCl$

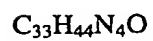
MW = 531.57

IR: (KBr) 3413, 2965, 2670, 1649, 1546  $cm^{-1}$ .

**EXAMPLE 9 : 3-[1,4']Bipiperidinyl-1'-ylmethyl-2-phenyl-quinoline-4-carboxylic acid ((S)-1,2,2-trimethyl-propyl)-amide**

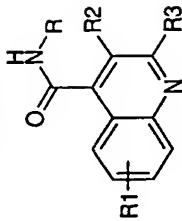
539 mg (0.94 mmol) of 3-[1,4']bipiperidinyl-1'-ylmethyl-2-phenyl-quinoline-4-carboxylic acid dihydrochloride (compound of Description 6), 202 microliters (1.5 mmol) of (S)-1,2,2-trimethyl-propylamine (Lancaster), 570 mg (1.5 mmol) of HBTU, 610 microliters (4.4 mmol) of triethylamine were dissolved in 12 ml THF and 8.5 ml of  $CH_2Cl_2$  and the mixture was refluxed for 18 h. The solvent was concentrated, the residue was dissolved in methylene chloride, washed with water, then with 0.5 N

aqueous NaOH, again with water, and the organic phase was dried over MgSO<sub>4</sub>. After concentration of the solvent, the residue was purified by flash chromatography over 40 g of silicagel (eluent EtOAc/MeOH/NH<sub>4</sub>OH : 90/10/0.1), affording 290 mg (yield 56%) of the title compound as a beige amorphous solid.



MW = 512.74

Table 1



R<sub>1</sub> = H; R<sub>3</sub> = Ph

Ex.	R	R <sub>2</sub>	Molecular Formula	Molecular Weight	Melting Point (°C)
1			C <sub>28</sub> H <sub>38</sub> N <sub>4</sub> O.2HCl	531.57	204-206
2			C <sub>28</sub> H <sub>36</sub> N <sub>4</sub> O	444.63	215-217
3			C <sub>27</sub> H <sub>34</sub> N <sub>4</sub> O.2HCl	503.52	198-200
4			C <sub>29</sub> H <sub>38</sub> N <sub>4</sub> O.2HCl	531.57	235-238
5			C <sub>37</sub> H <sub>42</sub> N <sub>4</sub> O <sub>2</sub>	574.76	144-146




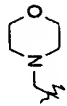
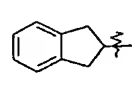
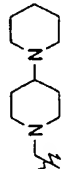

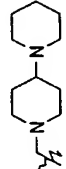

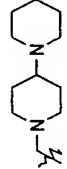

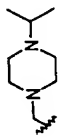
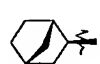
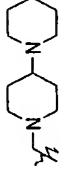
6			$C_{36}H_{40}N_4O_2$	560.74	98-100
7			$C_{27}H_{33}N_3O_2$	431.58	207-209
8			$C_{36}H_{40}N_4O$	544.74	amorphous solid
9			$C_{33}H_{44}N_4O$	512.74	amorphous solid
10			$C_{37}H_{46}N_4O$	562.80	219-220
11			$C_{30}H_{38}N_4O$	470.66	161-163
12			$C_{34}H_{42}N_4O$	522.73	amorphous solid



Table 2

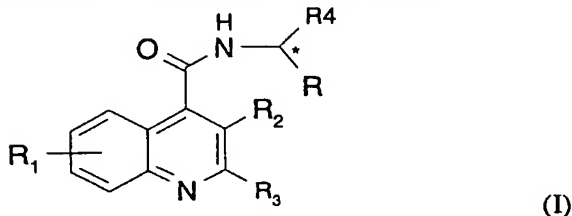
Example	<sup>1</sup> H NMR (Solvent) δ ppm
1	δ (DMSO-d <sub>6</sub> ) (+TFA): 0.99(3H); 1.00(3H); 1.21(9H); 1.90(1H); 2.50-2.60(6H); 2.70-3.10(2H); 3.33(1H); 3.74 and 3.79(2H); 4.00-4.11(1H); 7.50-7.65(5H); 7.70(1H); 7.85(1H); 7.90(1H); 8.11(1H); 8.41(1H).
2	δ (DMSO, 353 K): 1.04(6H); 1.18(6H); 2.00(1H); 2.80-2.30(9H); 3.27(2H); 3.70(2H); 7.68-7.45(6Har); 7.80(1Har); 7.89(1Har); 8.05(1Har); 8.40(1H exch with D <sub>2</sub> O);.
3	δ (DMSO): 0.95(6H); 1.27(6H); 2.35-2.20(8H); 2.65(1H); 3.60(2H); 4.23(1H); 7.51-7.41(3Har); 7.55(2Har); 7.62(1Har); 7.76(1Har); 7.89(1Har); 8.01(1Har); 8.30(1H exch with D <sub>2</sub> O).
4	δ (DMSO): 0.87(6H); 0.95(6H); 1.63-1.48(4H); 2.20-2.00(8H); 2.49(1H); 3.59(2H); 3.95(1H); 7.51-7.41(3Har); 7.55(2Har); 7.67(1Har); 7.78(1Har); 7.87(1Har); 8.01(1Har); 8.50(1H exch with D <sub>2</sub> O).
5	δ (CDCl <sub>3</sub> ): 0.55-1.03(2H); 1.12-2.40(17H and 1Hexch with D <sub>2</sub> O); 2.55(2H); 2.82(2H); 3.30-3.80(1H); 3.64(1H); 5.63(2H); 6.97-7.22(3Har); 7.32-7.57(6Har); 7.62(1Har); 7.75(1Har); 8.15(1Har); 8.37(1Har); 9.40(1Hexch with D <sub>2</sub> O).
6	δ (DMSO): 0.95-1.52(6H); 1.53-1.82(4H); 1.84-2.14(4H); 2.45-2.72(4H); 2.74-3.12(3H); 3.35(1H); 3.55(2H); 4.46(1Hexch with D <sub>2</sub> O); 5.64(1H); 7.12-7.60(9Har); 7.65(1Har); 7.78(1Har); 8.00(2Har); 9.08(1Hexch with D <sub>2</sub> O).
7	δ (CDCl <sub>3</sub> ): 1.02(9H); 1.25(3H); 2.19(4H); 3.49(4H); 3.76(2H); 4.36(1H); 7.38-7.98(7Har and 1Hexch with D <sub>2</sub> O); 8.07(1Har); 8.13(1Har).
8	δ (CDCl <sub>3</sub> ): 0.87-1.28(2H); 1.30-1.92(8H); 2.05(1H); 2.21-2.60(6H); 2.35-3.12(4H); 3.53(2H); 6.65(2H); 5.06(1H); 7.05-7.32(4Har); 7.35-7.52(5Har); 7.58(1Har); 7.73(1Har); 7.13(2Har); 8.80(1Hexch with D <sub>2</sub> O).
9	δ (CDCl <sub>3</sub> ): 1.01(9H); 1.28(3H); 1.00-1.98(12H); 2.15(1H); 2.28-2.56(5H); 2.88(1H); 3.71(2H); 4.35(1H); 7.45-7.62(6Har); 7.72(1Har); 8.12(1Har); 8.49(1Hexch with D <sub>2</sub> O).
10	δ (CDCl <sub>3</sub> ): 1.10-2.32(27H); 2.38(4H); 2.67(2H); 3.68(2H); 4.42(1H); 7.35-7.80(7Har and 1Hexch with D <sub>2</sub> O); 8.00(1Har); 8.13(1Har).
11	δ (DMSO 353 K): 0.90(6H); 1.50-1.20(5H); 1.67(1H); 1.80(2H); 2.00(2H); 2.20(8H); 2.50(1H); 3.59(2H); 4.00(1H); 7.50-7.42(3Har); 7.57(2Har); 7.62(1Har); 7.76(1Har); 7.89(1Har); 8.01(1Har); 8.26(1H exch with D <sub>2</sub> O).
12	δ (CDCl <sub>3</sub> ): 1.07-2.18(21H); 2.28-2.54(6H); 2.68(2H); 3.68(2H); 4.09(1H); 7.38-7.66(6Har); 7.73(1Har); 7.85(1Hexch with D <sub>2</sub> O); 8.02(2Har).

Table 3

Example	Chemical names of examples
1	3-(4-Isopropyl-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((R,S)-1,2-dimethyl-propyl)-amide dihydrochloride
2	3-(4-Isopropyl-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid isobutyl-amide
3	3-(4-Isopropyl-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid isopropylamide
4	3-(4-Isopropyl-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid (1-ethyl-propyl)-amide
5	3-(4-Hydroxy-[1,4]bipiperidinyl-1'-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-1,2,3,4-tetrahydro-naphthalen-1-yl)-amide
6	3-(4-Hydroxy-[1,4]bipiperidinyl-1'-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid (S)-indan-1-ylamide
7	3-Morpholin-4-ylmethyl-2-phenyl-quinoline-4-carboxylic acid ((S)-1,2,2-trimethyl-propyl)-amide
8	3-[1,4]Bipiperidinyl-1'-ylmethyl-2-phenyl-quinoline-4-carboxylic acid indan-2-ylamide
9	3-[1,4]Bipiperidinyl-1'-ylmethyl-2-phenyl-quinoline-4-carboxylic acid ((S)-1,2,2-trimethyl-propyl)-amide
10	3-[1,4]Bipiperidinyl-1'-ylmethyl-2-phenyl-quinoline-4-carboxylic acid adamantan-2-ylamide
11	3-(4-Isopropyl-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid cyclohexylamide
12	3-[1,4]Bipiperidinyl-1'-ylmethyl-2-phenyl-quinoline-4-carboxylic acid (1S,2S,4R)-bicyclo[2.2.1]hept-2-ylamide

## Claims:

1. A compound, or a solvate or a salt thereof, of formula (I):



wherein R is linear or branched alkyl;

R<sub>1</sub> represents hydrogen or up to four optional substituents selected from the list consisting of: C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkenyl, aryl, C<sub>1-6</sub> alkoxy, hydroxy, halogen, nitro, cyano, carboxy, carboxamido, sulphonamido, C<sub>1-6</sub> alkoxycarbonyl, trifluoromethyl, acyloxy, phthalimido, amino or mono- and di-C<sub>1-6</sub> alkylamino;

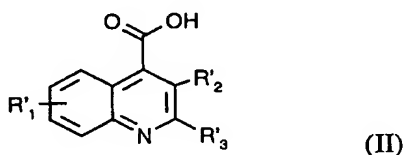
R<sub>2</sub> represents a moiety  $-(CH_2)_n-NY_1Y_2$  wherein n is an integer in the range of from 1 to 9, Y<sub>1</sub> and Y<sub>2</sub> are independently selected from hydrogen; C<sub>1-6</sub>-alkyl; C<sub>1-6</sub> alkyl substituted with hydroxy, C<sub>1-6</sub> alkylamino or bis (C<sub>1-6</sub> alkyl) amino; C<sub>1-6</sub>-alkenyl; aryl or aryl-C<sub>1-6</sub>-alkyl or Y<sub>1</sub> and Y<sub>2</sub> together with the nitrogen atom to which they are attached represent an optionally substituted N-linked single or fused ring heterocyclic group;

R<sub>3</sub> is branched or linear C<sub>1-6</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>4-7</sub> cycloalkylalkyl, optionally substituted aryl, or an optionally substituted single or fused ring aromatic heterocyclic group; and

R<sub>4</sub> represents hydrogen or alkyl or R<sub>4</sub> and R together with the carbon atom to which they are attached form an optionally substituted C<sub>3-12</sub> cycloalkyl group.

2. A compound according to claim 1, wherein R is C<sub>1-6</sub> alkyl.
3. A compound according to claim 1 or claim 2, wherein R is tert-butyl.
4. A compound according to claim 1, wherein R<sub>4</sub> and R together with the carbon atom to which they are attached represent a C<sub>3-12</sub> cycloalkyl group fused to either another cycloalkyl group or to an aryl group.
5. A compound according to any one of claims 1 or 4, wherein R<sub>4</sub> and R together with the carbon atom to which they are attached represent a C<sub>5</sub> or C<sub>6</sub> cycloalkyl group fused to one or more C<sub>5</sub> or C<sub>6</sub> cycloalkyl groups

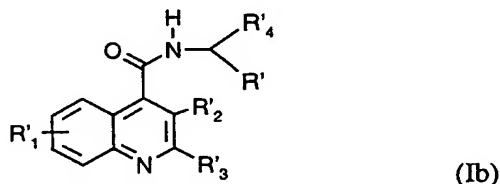
6. A compound according to claim 5, wherein R<sub>4</sub> and R together with the carbon atom to which they are attached represent 2-adamantyl or 2-bicyclo[2.2.1]heptane.
7. A compound according to any one of claims 1 or 4, wherein R<sub>4</sub> and R together with the carbon atom to which they are attached represent indan-1-yl, indan-2-yl or 1, 2, 3, 4 -tetrahydronaphthalen-1-yl.
8. A compound according to any one of claims 1 or 7, wherein R<sub>4</sub> is C<sub>1-6</sub> alkyl, for example methyl.
9. A compound according to any one of claims 1 or 8, wherein R<sub>1</sub> represents hydrogen, C<sub>1-6</sub> alkoxy, for example methoxy or hydroxy.
10. A compound according to any one of claims 1 or 9, wherein R<sub>1</sub> represents hydrogen.
11. A compound according to any one of claims 1 or 10, wherein NY<sub>1</sub>Y<sub>2</sub> represents an optionally substituted N-linked single or fused ring heterocyclic group.
12. A compound according to claim 1, selected from examples 1 to 12 as disclosed herein.
13. A process for the preparation of a compound of formula (I), or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (II) or an active derivative thereof:



wherein R'<sub>1</sub>, R'<sub>2</sub> and R'<sub>3</sub> are R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> respectively as defined in relation to formula (I) or a group convertible to R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> respectively; with a compound of formula (III):



wherein R' and R<sub>4</sub>' are R and R<sub>4</sub> as defined for formula (I) or a group or atom convertible to R and R<sub>4</sub> respectively; to form a compound of formula (Ib):



wherein R', R'<sub>1</sub>, R'<sub>2</sub>, R'<sub>3</sub> and R'<sub>4</sub> are as defined above, and thereafter carrying out one or more of the following optional steps:

- (i) converting any one of R', R'<sub>1</sub>, R'<sub>2</sub>, R'<sub>3</sub> and R'<sub>4</sub> to R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> or R<sub>4</sub> respectively as required, to obtain a compound of formula (I);
- (ii) converting a compound of formula (I) into another compound of formula (I);
- and
- (iii) preparing a salt of the compound of formula (I) and/or a solvate thereof.

14. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

15. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use as an active therapeutic substance.

16. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the treatment or prophylaxis of the Primary and Secondary Conditions.

17. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of the Primary and Secondary Conditions.

18. A method for the treatment and/or prophylaxis of the Primary and Secondary Conditions in mammals, particularly humans, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective, non-toxic pharmaceutically acceptable amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 99/09156

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D215/52 A61K31/4725 C07D401/06 A61K31/4709 A61P25/00  
A61P11/00 A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	GIARDINA G A M ET AL: "Discovery of a Novel Class of Selective Non-Peptide Antagonists for the Human Neurokinin-3 Receptor. 2. Identification of (S)-N-(1-Phenylpropyl)-3-hydroxy-2-phenylquinoline-4-carboxamide (SB 223412)" J. MED. CHEM. (JMCMAR,00222623);1999; VOL.42 (6); PP.1053-1065, XP000882756 SmithKline Beecham S.p.A.;Department of Medicinal Chemistry; Baranzate; 20021; Italy (IT) page 1055; example 56	1-17
P,Y	WO 98 52942 A (RAVEGLIA LUCA FRANCESCO ;GRAZIANI DAVIDE (IT); GRUGNI MARIO (IT);) 26 November 1998 (1998-11-26) claim 1	1-17
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*G\* document member of the same patent family

Date of the actual completion of the international search

6 March 2000

Date of mailing of the international search report

31.03.00

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Gettins, M

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 99/09156

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 21680 A (SMITHKLINE BEECHAM SPA ;GIARDINA GIUSEPPE ARNALDO MARI (IT); GRUGN) 19 June 1997 (1997-06-19) claim 1 ---	1-17
Y	WO 97 19926 A (SMITHKLINE BEECHAM SPA ;GIARDINA GIUSEPPE ARNALDO MARI (IT); GRUGN) 5 June 1997 (1997-06-05) claim 1 ---	1-17
Y	WO 97 19928 A (SMITHKLINE BEECHAM SPA ;GIARDINA GIUSEPPE ARNALDO MARI (IT); FARIN) 5 June 1997 (1997-06-05) claim 1 ---	1-17
Y	GIARDINA G A M ET AL: "2-PHENYL-4-QUINOLINECARBOXYAMIDES: A NOVEL CLASS OF POTENT AND SELECTIVE NON-PEPTIDE COMPETITIVE ANTAGONISTS FOR THE HUMAN NEUROKININ-3 RECEPTOR" JOURNAL OF MEDICINAL CHEMISTRY,US,AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 39, no. 12, 7 June 1996 (1996-06-07), pages 2281-2284, XP000197077 ISSN: 0022-2623 table 1 ---	1-17
Y	WO 96 02509 A (SMITHKLINE BEECHAM FARMA ;FARINA CARLO (IT); GIARDINA GIUSEPPE ARN) 1 February 1996 (1996-02-01) claim 1 ---	1-17
Y	WO 95 32948 A (SMITHKLINE BEECHAM FARMA ;FARINA CARLO (IT); GIARDINA GIUSEPPE ARN) 7 December 1995 (1995-12-07) claim 1 -----	1-17

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 99/09156

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claim 18 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No  
PCT/EP 99/09156

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9852942 A	26-11-1998	IT 1295358 B IT MI972775 A AU 8209898 A	12-05-1999 16-06-1999 11-12-1998
WO 9721680 A	19-06-1997	IT MI952461 A IT MI961689 A AU 1031797 A BG 102558 A BR 9611820 A CA 2238298 A CN 1207730 A CZ 9801579 A EP 0876347 A NO 982331 A PL 326967 A SK 66798 A	26-05-1997 02-02-1998 03-07-1997 31-03-1999 13-07-1999 19-06-1997 10-02-1999 16-12-1998 11-11-1998 22-07-1998 09-11-1998 11-01-1999
WO 9719926 A	05-06-1997	IT MI952462 A IT MI961688 A AU 1031897 A BG 102557 A BR 9611757 A CA 2238328 A CN 1207729 A CZ 9801580 A NO 982333 A PL 326928 A SK 66898 A	26-05-1997 02-02-1998 19-06-1997 31-03-1999 06-04-1999 05-06-1997 10-02-1999 14-10-1998 22-07-1998 09-11-1998 02-12-1998
WO 9719928 A	05-06-1997	AU 1031997 A BR 9611729 A CA 2238312 A CN 1207728 A CZ 9801581 A EP 0876348 A NO 982332 A PL 326927 A	19-06-1997 06-04-1999 05-06-1997 10-02-1999 14-10-1998 11-11-1998 22-05-1998 09-11-1998
WO 9602509 A	01-02-1996	IT 1270615 B	07-05-1997
WO 9532948 A	07-12-1995	IT MI941099 A IT MI950494 A AP 578 A AU 1216299 A AU 699319 B AU 2616495 A BG 101008 A BG 103181 A BR 9507788 A CA 2191352 A CA 2257662 A CZ 9603470 A EP 0804419 A EP 0940391 A FI 964712 A FI 990268 A HU 76286 A JP 10500697 T	27-11-1995 16-09-1996 26-03-1997 25-03-1999 03-12-1998 21-12-1995 29-08-1997 30-09-1999 23-09-1997 07-12-1995 07-12-1995 15-10-1997 05-11-1997 08-09-1999 23-01-1997 10-02-1999 28-07-1997 20-01-1998

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No  
PCT/EP 99/09156

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9532948 A		NO 965036 A	24-01-1997
		NO 991813 A	24-01-1997
		NZ 287442 A	27-05-1998
		PL 317381 A	01-04-1997
		RO 114445 A	30-04-1999
		SK 4799 A	11-06-1999
		SK 151496 A	09-07-1997
		US 5811553 A	22-09-1998
		ZA 9504269 A	14-05-1996